REMARKS

Claims 32-33 have been rejected under 35 U.S.C. §112, first paragraph. Claim 32 has been cancelled. Claim 33 has been amended to specifically recite cyclodextrin as an additional component within the formulation. The specification clearly supports and enables the use of cyclodextrin in the formulation.

Claims 32-33, 43, 44, and 46 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. Claim 32 has been cancelled. Claim 33 no longer depends from Claim 32 and thus does not include the limitation "an agent." Claim 34 has been amended to correct the term erectile and substitute the correct term "sexual." In Claim 43, the term "beneficial" has been deleted. In Claims 44 and 46, the basis for concern was resolved by correcting the typographical error as to the base claim.

Claim 43 stands rejected under 35 U.S.C. §102 (b) as being anticipated by Alam et al. Alam et al. teaches misoprostol compositions for use in treatment of allergic responses. Claims 43-47 have been cancelled by the present amendment. New claims 48 and 49 present a new recitation of a pharmaceutical composition described in the present application. A pharmaceutical composition making use of misoprostol and alprostadil was present in Claim 45. New Claim 48 recites that "penetration of the alprostadil to underlying tissue is facilitated by the misoprostol compound." This synergic action is taught by the inventors at the bottom of page 3 of the patent application and is neither disclosed, suggested nor taught by the prior art references cited against the present application. For these reasons, Applicants submit that Claims 48 and 49 are in condition for allowance.

Claims 27-42 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Lowrey, Neal, Nahoum, and Buyuktimkin et al. in view of El-Rashidy and Reilly. The invention of Claim 27 includes using a topical formulation using as a primary vasoactive agent, misoprostol or misoprostol acid, for topical administration to the clitoris or vagina of the female subject in

need of treatment for sexual dysfunction. The references as a whole or individually fail to disclose this invention.

The patent to Neal is solely directed to treatment of male erectile dysfunction. The treatments focus on getting the active agent to the urethral area. Neal's preferred method of administration is with a suppository for melting or dissolving in the urethra. A slight mention of topical administration by dripping a solution of the composition directly on the urethral meatus is found at column 10, lines 33-35. But there is no explanation or example to suggest that this method would even work on male subjects. Again the urethral area is the target. To those in the art, Neal has suggested a formulation that takes effect in the urethra of a male subject, in particular, a formulation that includes 15-hydroxyprostaglandindehydrogenase inhibitor. Unlike the case for females, the urethra traverses the male sex organ being treated. Therefore, Neal has no apparent applicability to females.

Nahoum teaches formulations for use in treating both male and female sexual dysfunction. However, the primary active in Nahoum's formulation are H_2 and H_3 agonists. While Nahoum lists a number of other components that may be added to the formulation, including vasoactive agents, it is clear from the claims and specifications that the H_2 and H_3 agonists are the primary active and that other agents are considered secondary agents that may be included in the formulation. (See column 25, lines 37-48). In view of the teachings of Neal and Nahoum, treatment of female subjects for sexual dysfunction would rely upon H_2 and H_3 agonists as the primary agent.

Referring now to Lowrey, it is noted that female sexual response includes vasodilation and engorgement of the genitalia. Lowrey uses this knowledge so as to make his orally administered treatment available for use by male or females. Whatever parallels there may be between the response of males and female genitalia, and while both males and females have the same anatomy for receiving oral administration through the mouth, it is clear that females lack a penis. Whereas males have a urethra passing through the sex organ to be

stimulated, the female anatomy includes a urethra that is distinct from the sex organs. Prior art disclosures of transurethral or topical administration targeting the urethra in men have not been shown to suggest any corresponding treatment in females. Thus, Lowrey only suggests that oral administration helpful in male sexual dysfunction might be tried in females. Indeed, example 5 in Lowrey is a mere prophetic example suggesting that one might try using the oral formulation on female subjects. Applicants find no fair suggestion in the cited art that topical treatments for sexual dysfunction directed toward the urethra in a male penis corresponds to any known treatment in a female.

The Examiner concedes that "the primary references do not expressly teach the application of the topical prostaglandin composition in a method of treating female sexual dysfunction to the vagina or clitoris." Applicants respectfully submit that neither is there an implicit suggestion or teaching of topical administration to the vagina or clitoris of a formulation whose primary vasoactive agent is misoprostol or misoprostol acid. Turning to the remaining references we note that these references lack such a teaching as well, therefore Claims 27 and all claims depending therefrom should be allowed.

Buyuktimkin et al. is one of the primary references considered by the Examiner and does not relate to sexual dysfunction either male or female. El-Rashidy lacks any discussion of the treatment of females or female sexual dysfunction. Reilly also does not discuss sexual dysfunction treatments. In view of the art as a whole at the time of the invention, the invention as claimed in Claim 27 and all claims depending therefrom should be allowed.

Claims 41 and 42 more broadly recite use of a mixture including misoprostol or misoprostol acid. Claim 41 has been amended to recite "topically" administering the mixture to a female subject. Of the references relating to sexual dysfunction, Neal and El-Rashidy concern male sexual dysfunction, i.e. erectile dysfunction. Neal is directed toward getting vasodilator to the urethral area. El-Rashidy discloses use of absorption enhancers to

facilitate getting vasodilator through the skin of the penis to the underlying tissue. Both are addressed to the unique characteristics of the male sex organ.

Lowrey suggests that an oral administration suitable for male sexual dysfunction may also be tried for females.

Nahoum discloses a variety of compositions and has demonstrated effectiveness of using injections or intraurethral administration to achieve some degree of erectile penile response. While Nahoum suggests that the compositions may be useful for female sexual dysfunction, there is no disclosure or suggestion of an appropriate administration method for use in females. Nahoum does not disclose any results with respect to female sexual dysfunction. A finding of obviousness requires that the prior art show a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q. 2d 1016 , 1022 (Fed.Cir.1991) Given that Nahoum provides no discussion or teaching of a method of administration and no test results (let alone successful results) on female subjects, there is no teaching of Applicants' method nor a showing that it would be expected to succeed. Neal and El-Rashidy relating to male erectile dysfunction and Buyuktimkin and Reilly lacking discussion of topical treatment methods do not satisfy the deficiencies of Nahoum. Lowrey discloses oral administration and thus fails to establish a reasonable expectation of success for topical administration to females. Successful topical procedures for sexual dysfunction in the references were directed to the male penis, a sex organ surrounded by skin and having a urethra. The cited prior art references fail to disclose topical administration methods and results with respect to females. For these reasons, Applicants submit that Claims 41 and 42 are patentable over the art of record.

In rejecting a claim for obviousness, the examiner is reminded to consider the teachings of the prior art to one of ordinary skill in the art at the time of the invention without resorting to guidance from Applicants' invention. A brief examination of "hindsight" law would be helpful. In *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q. 2nd , 1434, 1438 (Fed. Cir. 1988) the Federal Circuit held:

> When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself...Something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination...

The references cited by the Examiner while acknowledging female sexual dysfunction, fail to disclose results to suggest a reasonable probability of success from topical treatments. Moreover, there is no disclosure of a method of treating through topical administration the female anatomy, unique as it is from the male anatomy.

In considering any individual reference and what it teaches, the examiner must consider the teaching as a whole. To selectively extract features taught by Applicants or to ignore the whole teaching of the references and the knowledge of those in the art at the time is improper. "It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Hedges*, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). Lowrey does not stand for the proposition that any male treatments for sexual dysfunction may be successfully used on women. Looking at the whole patent, it merely states that there are similarities in sexual response and that the oral treatment for males can be tried in women. Applicants respectfully submit that an obviousness rejection is not properly supported by the prior art references.

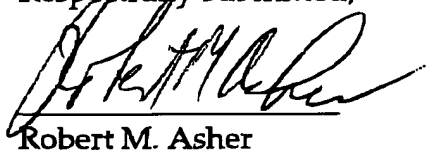
Claims 43-47 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over Nahoum. Claims 43-47 have been cancelled making this rejection moot.

New claims 50-54 have been added to more fully cover Applicants' invention. Claim 50 recites a formulation that lacks a non-misoprostol penetration enhancer and in which penetration to the underlying tissue is facilitated by the misoprostol or misoprostol acid. The Examiner indicated in

discussing the Declaration of Mr. Fotinos that, "The data demonstrates the effectiveness of misoprostol formulation, in absence of any organic solvent or penetration enhancer, to be more effective than that of prostaglandin E_1." Applicants respectfully submit that Claims 50-54 should be allowed.

For all the foregoing reasons, Applicants submit that the claims currently pending in the application are patentable over the art of record and early notice to that effect is respectfully solicited.

Respectfully submitted,



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